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Cardiorespiratory fitness levels and moderators in people with HIV: a systematic review and meta-analysis

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Abstract

Cardiorespiratory fitness (CRF) is a modifiable risk factor for cardiovascular disease and premature mortality. CRF levels and moderators among people living with HIV (PLWH) are unknown. The aim of the current meta-analysis was to (1) determine mean CRF in PLWH and compare levels with age- and gender-matched healthy controls (HCs), (2) explore moderators of CRF,3and (4) explore moderators of CRF outcomes following physical activity (PA) interventions. Major electronic databases were searched systematically for articles reporting CRF expressed as maximum or peak oxygen uptake (ml/min/kg) in PLWH. A random effects meta-analysis calculating the pooled mean CRF including subgroup- and meta-regression analyses was undertaken. Across 21 eligible studies, the CRF level was 26.4 ml/kg/min (95%CI=24.6 to 28.1) (n=1,010; mean age =41years). There were insufficient data to compare CRF levels with HCs. A higher body mass index (β=-0.99, 95%CI=-1.93 to -0.06, P=0.04), older age (β=-0.31, 95%CI=-0.58 to -0.04, P=0.02) and the presence of lipodystrophy (β=-4.63, 95%CI=-7.88 to -1.39, P=0.005) were significant moderators of lower CRF levels. Higher CD4+ counts (β=0.004, 95%CI=0.0007 to 0.007, P=0.016), supervised interventions (P<0.001) and interventions with a lower frequency of weekly sessions (2 or 3 versus 4 times) (P<0.001) predicted a better CRF-outcome following PA. CRF levels of PLWH are among the lowest in comparison to other vulnerable populations. More research on the most optimal physical activity intervention characteristics is needed.

Keywords: aerobic fitness; physical activity; exercise; HIV; AIDS

Introduction

People living with HIV (PLWH) have higher levels of morbidity and mortality than the general population (Farahani et al., 2016). The non-AIDS related mortality rates are largely attributable to cardiovascular disease (Farahani et al., 2016). Current hypotheses link the increased incidence of these comorbidities to side-effects of antiviral therapy (Dillon et al., 2013; El-Sadr, 2007), HIV-related chronic inflammation (Hearps et al., 2014) and modifiable lifestyle factors, such as increased tobacco use (Lifson and Lando, 2012) and decreased physical activity (Schuelter-Trevisol et al., 2012). There is evidence in PLWH that participation in physical activity might reduce cardio-metabolic risk factors and improve quality of life (Fillipas et al., 2010; Gomes-Neto et al., 2013; Gomes Neto et al., 2013; Leach et al., 2015; Neto et al., 2015; O'Brien et al., 2008). In the general population, there is robust evidence demonstrating that low cardiorespiratory fitness (CRF, the ability of the circulatory and respiratory systems to supply oxygen to working muscles during sustained physical activity) is a strong predictor for CVD [relative risk (RR)=1.56; 95% confidence interval (CI)=1.39-1.75; p<0.001] and all-cause mortality (RR=1.70; 95%CI=1.51-1.92; *P*<0.001) (Kodama et al., 2009). Exercise interventions aiming to improve CRF should therefore be a key component of preventing and treating CVD and reducing associated mortality (Barry et al., 2014).

A recent meta-analysis (O'Brien et al., 2016) into the effectiveness of aerobic exercise for PLWH showed a significant improvement in maximum oxygen uptake (VO_2max), which is the gold-standard for assessing CRF, of 2.63 mL/kg/min following aerobic exercise interventions compared with control conditions. These findings clearly highlight that improving CRF is a feasible and effective strategy for reducing cardio-metabolic risk among PLWH. Despite the clinical significance of measuring CRF in PLWH, it remains unclear exactly what CRF levels are, and what moderates CRF levels in PLWH. Moreover, it remains unclear if PLWH have different CRF levels versus age- and gender matched controls. Pooled analyses exploring subgroup differences in CRF among PLWH are highly relevant as they enable risk stratification. Pooling data also allows for more thorough investigation of the effect of demographic variables (e.g., age and gender), clinical variables (e.g., CD4+ count), assessment variables (e.g., maximal versus submaximal and running versus cycling) and treatment variables (antiviral exposure or not) on CRF levels. Finally, whilst a previous meta-analysis (O'Brien et al., 2016) showed that physical activity interventions can improve CRF, no meta-regression analyses has been conducted to investigate moderators which might influence this and inform the rehabilitation of PLWH.

In order to address these current gaps in the literature, we conducted a meta-analysis with the following aims: (1) investigate the mean pooled CRF level in PLWH and compare CRF levels where possible with age- and gender-matched healthy controls, (2) explore moderators of CRF levels in PLWH, and (3) explore moderators of CRF outcomes following physical activity interventions.

Methods

This systematic review adhered to the PRISMA statement (Moher et al., 2009).

Search procedure

Two researchers (DV and BS) searched PubMed, Embase and CINAHL from database inception to May 15, 2016. Key words used were "cardiorespiratory" OR "aerobic" AND "HIV" OR "AIDS" in the title, abstract or index term fields. Manual searches were also conducted using the reference lists from recovered articles.

Eligibility criteria

Inclusion criteria were: (a) inclusion of adult participants with a diagnosis of HIV or AIDS, (b) measurement of CRF (mean ± standard deviation) expressed as maximal oxygen uptake, VO_2max or VO_2peak (ml/kg/min) and assessed with a maximal exercise test or estimated with a sub-maximal exercise test, (c) interventional (randomized controlled trials, clinical controlled trials, one-arm pre-test post-test) and observational (prospective or cross sectional) studies conducted in any setting (inpatients, outpatients or community patients) with or without a healthy control group. All physical activity intervention studies were included. Physical activity was defined in accordance with Caspersen et al.(Caspersen et al., 1985) as any interventions that use bodily movement produced by skeletal muscles and which requires energy expenditure. Exercise is defined as physical activity interventions that were planned, structured, repetitive and purposive, in the sense that improvement or maintenance of physical fitness was an objective (Caspersen et al., 1985). No additional exclusion criteria were applied.

Study selection

After the removal of duplicates, two reviewers (DV and BS) screened titles and abstracts of all potentially eligible articles. Both authors applied eligibility criteria, and a list of full text articles was developed. Two reviewers (DV and BS) then applied eligibility criteria and a final list of included articles was reached through consensus. In case of overlap the most recent study was included.

Data extraction

Data extracted for exploring moderators of CRF included assessment variables (maximal versus submaximal and running versus cycling), geographical region (North-America versus South-America versus Europe versus Africa versus Asia versus Oceania), setting (inpatients versus outpatients versus community patients), participants characteristics including mean age (years), % male, % Caucasian, mean illness duration (years), mean antiviral treatment duration (months), mean body mass index, mean lean body mass loss (kg), mean maximal or peak oxygen uptake (ml/min/kg), mean CD4 count (cells/mm³), mean HIV viral load (log^{10} copies/mL), with or without lipodystropy, with or without opportunistic infections, % with diabetes, % smoking, % on antiviral therapy. If age- and gender matched healthy control data were available, in addition to the primary outcome, age and % male of the healthy control groups were collected. For the intervention analyses, data extracted included duration (number of weeks), frequency (times per week), intensity (low versus moderate versus high following the American College of Sports Medicine criteria (2009)), and type (aerobic exercise only vs mixed) of the physical activity intervention, whether the intervention was supervised or not and qualified versus non-qualified providers. Providers of physical activity interventions were considered experts when they had at a minimum a bachelor-level degree in physical therapy, exercise physiology or a similar qualification that included education in physical activity prescription and assessment.

Methodological study appraisal

Two authors (DV and BS) independently completed methodological quality assessment of included articles using the Newcastle–Ottawa Scale (NOS) (Wells et al., 2000). If any disagreement arose, a third author (JM) was available for mediation. The NOS provides an assessment of the methodological quality of non-randomised trials, and its content validity and reliability have been established (Wells et al., 2000). Included studies are judged on 9 items across 3 key areas: selection of the participants, comparability of the participants, and outcomes. Each study receives an overall score for methodological quality of up to 9 points (one for each item) with higher scores indicating better quality.

Statistical analyses

Random-effects meta-analyses were conducted using Comprehensive Meta-Analysis software (Version 3, Biostat, Englewood, New Jersey). First, we pooled the mean CRF level among PLWH and where possible compared this to healthy controls (aim 1). Second, we compared baseline CRF levels between geographical regions (North-America versus South-America versus Europe versus Africa versus Asia versus Oceania), study settings (inpatients versus outpatients versus community settings), assessment variables (maximal versus submaximal and running versus cycling) and clinical variables (with versus without lipodystrophy and with versus without opportunistic infections) and conducted meta-regression analyses according to age (year), gender (% male), ethnicity (% Caucasian), illness duration (years), antiviral treatment duration (months), mean body mass index, lean body mass loss (kg), mean CD4 count (cells/mm³), mean HIV viral load (log^{10} copies/mL), % with diabetes, % smoking, and % on antiviral therapy (aim 2). We used the Hedges' g statistic and standard mean differences (SMD) and their 95% confidence intervals (CIs) for calculating the estimates of the physical activity interventions effects on CRF levels. Where sufficient data was available, exploratory meta-regression analyses were undertaken to investigate the influence on physical activity outcomes of mean age (years), gender (% male), ethnicity (% Caucasian), illness duration (years), mean body mass index, mean CD4 count (cells/mm³), mean HIV viral load (log^{10} copies/mL), % on antiviral therapy, and duration (number of weeks), frequency (times per week), of the physical activity intervention. We also explored whether the intervention effect differed according to different intensity levels (low versus moderate versus high), type (aerobic exercise only vs mixed), whether or not the intervention was supervised or not and whether or not providers were qualified or not (aim 2). Finally, we explored changes in CRF following physical activity interventions in PLWH calculating Hedges'g and the mean CRF change (aim 3). Statistical heterogeneity was assessed using the I^2 statistic. Publication bias was assessed with the Begg and Mazumdar (1994) test (Begg and Mazumdar, 1994). For all analyses we calculated the trim and fill adjusted analysis (Duval and Tweedie, 2000) to remove the most extreme small studies from the positive side of the funnel plot, and recalculated the effect size at each iteration, until the funnel plot was symmetric about the (new) effect size.

Results

Search results and flow of studies through the review

A total of 1,409 records were identified. After screening titles and application of the eligibility criteria, 21 studies(Baigis et al., 2002; Cade et al., 2003; Cade et al., 2013; Cutrono et al., 2015; Dolan et al., 2006; Ezema et al., 2014; Hand et al., 2008; Jaggers et al., 2014; MacArthur et al., 1993; Mangona et al., 2015; Mapstone et al., 2014; Mutimura et al., 2008; Neto et al., 2016; Oursler et al., 2009; Perna et al., 1999; Ramírez-Marrero et al., 2014; Raso et al., 2013; Smith et al., 2001; Sullivan et al., 2014; Terry et al., 2006; Thoni et al., 2002) were eligible for inclusion in the meta-analysis. Figure 1 presents the flow of studies through the review process.

Figure 1 here

Characteristics of included studies

Across the 21 studies, the final data set included 1,010 PLWH (N CRF values = 36). There were 14 interventional studies (N CRF values = 26) of which 3 one-arm pre- and post-test studies and 11 RCTs and 7 cross-sectional studies (N CRF values = 10). Five CRF values were assessed with maximal (n=31) and sub-maximal (n=5) exercise tests. Nine exercise tests were performed on a cycle ergometer and 27 on a treadmill. When looking at the settings in which the exercise tests took place, four CRF assessments were conducted among inpatients, one in outpatients and 12 in community patients. Other tests were performed in mixed or unknown settings. Twenty-five CRF values were assessed in North-American PLWH, 5 in South-American (all in Brazil) and 5 in African patients. Only one study was conducted in Europe (France). Among available studies, the mean age ranged from 32 to 58.9 years (N=36), the body mass index from 22.8 to 31 kg/m^2 (N=26) and years living with HIV infection from 4 to 17.6 years (N=12). The gender distribution was available for 34 CRF levels; 621 of 977 (63.6%) were male. The percentage of people from Caucasian ethnicity ranged from 0% to 93% (N=19). The presence of diabetes (N=5) ranged from 0 to 35.1%. The CD4+ count ranged from 104 to

663 cells/mm³ (N=28), the viral load from 2.3 to 4.4 log 10 copies/mL (N=6). There were no data on mean lean body mass loss and three studies reported on the mean antiviral treatment duration which ranged from 63 weeks to 45.2 months (Cade et al., 2003; Terry et al., 2006; Mutimuura et al., 2008). Details for all studies are provided in Table 1.

Table 1 here

Details for the interventional studies are provided in Table 2. In total 15 studies (n=369; mean age range=36-48 years) were included. Fourteen physical activity interventions were supervised throughout the intervention period. A qualified instructor was used in 6 of the identified studies. The duration of the intervention ranged from 6 to 26 weeks, the frequency of sessions from 2 to 4 times per week, the duration (time) of sessions from 20 to 120 min. In 9 interventions the intensity was increased up to vigorous levels. Eight interventions investigated aerobic exercise only while 7 were combined with resistance training.

Table 2 here

Methodological quality of included studies

The NOS score across the studies ranged from 3 to 8 with a mean of 5.8 (SD=2.2). Summary scores are presented in Tables 1.

Aim 1: cardiorespiratory fitness in people living with HIV versus controls

Across the 21 studies (including 36 CRF values) (n=1,010; mean age at study level= 41years), the pooled mean predicted VO_2 max or VO_2 peak was 27.4 ml/kg/min (95%CI = 25.8 to 29.0; I^2=99.6%; Kendall's tau=0.09, p=0.46; Egger=-5.1, p=0.15). Although there was no indication of publication bias, the trim-and-fill adjusted pooled mean predicted VO_2 max or VO_2 peak was 26.4 ml/kg/min (95%CI = 24.6 to 28.1) (N studies adjusted=5). There were insufficient data to compare differences in CRF levels between PLWH and age- and gender matched healthy controls.

Aim 2: Moderators of cardiorespiratory fitness in people living with HIV

Full details of the subgroup analyses of CRF levels are summarized in table 3. Higher CRF levels were found in maximal versus submaximal exercise tests (P<0.001), in treadmill versus cycle ergometer tests (P=0.028) and in people without (versus with) lipodystrophy (P<0.001).

When comparing geographical regions with each other we did find higher CRF levels in South-America versus Africa (z-value=8.2, $P<0.001$) and versus Europe (z-value=7.9, $P<0.001$).

Table 3 here

Higher body mass index (β =-0.99, 95%CI = -1.93 to -0.06, P=0.04), older age (β=-0.31, 95%CI = -0.58 to -0.04, P=0.02) and the presence of lipodystrophy (β=-4.63, 95%CI = -7.88 to -1.39, P=0.005) were significant moderators of lower CRF levels. Full details of all meta-regression analyses of CRF levels are summarized in table 4.

Table 4 here

Aim 3: Cardiorespiratory fitness outcomes and its moderators in people living with HIV following physical activity

The mean improvement in CRF following physical activity interventions was 3.43 ml/min/kg (95% CI=1.82 to 5.0). The Hedges' g was 0.82 (95%CI=0.48 to 1.16, $P<0.001$), which remained unchanged after trim-and-fill adjustment. In the meta-regression analysis only higher levels of CD4+ counts predicted a higher SMD. Better CRF outcomes were obtained in physical activity interventions that were supervised (versus not-supervised) ($P<0.001$) and with a lower frequency of weekly sessions (2 or 3 versus 4 times) ($P<0.001$). Bèta- and r^2-values of the meta-regressions are summarized in Table 5.

Table 5 here

Discussion

General findings

This is the first meta-analysis investigating mean CRF levels in PLWH. Our review identified 21 studies involving more than 1000 PLWH. The trim and-fill adjusted pooled mean CRF was 26.4 ml/kg/min (95%CI = 24.6 to 28.1, p<0.001). Although due to limited data available we could not compare the CRF levels with age- and gender matched healthy controls, the reported CRF levels are among the lowest reported within the clinical literature. For example, a previous meta-analysis (Davy Vancampfort et al., 2016) in almost 1000 people with severe mental illness (mean age= 35 years), a population known to be at high risk for CVD and premature mortality(D Vancampfort et al., 2016; Vancampfort et al., 2015c), the CRF level was 28.7 ml/kg/min (95%CI=27.3 to 30.0 ml/kg/min). This meta-analysis is also the first to demonstrate that older age, higher BMI, and the presence of lipodystrophy are associated with lower CRF levels among PLWH. Additionally, use of maximal (versus sub-maximal) and treadmill (versus cycle ergometer) testing protocols predicted higher CRF levels.

Knowledge of demographic and clinical variables associated with a lower CRF can help identify individuals at greatest need for intensive monitoring and intervention to improve CRF. The finding that older age was associated with lower CRF levels supports previous research in the general population (Parker et al., 2010), while there was also a suggestion that (P=0.06) lower CRF levels are found in studies with a lower percentage of male participants. Neither illness duration nor immunological parameters influenced CRF levels. However, the presence of lipodystrophy predicted lower baseline CRF levels. Previous research in PLWH reported a tendency that lipodystrophy might induce mitochondrial dysfunction in the skeletal muscle (Røge et al., 2002). Mitochondria are the main energy source for the cells and normal mitochondrial function is needed to permit normal muscle function (Zoll et al., 2002). An improvement in CRF in normal subjects is related to both an increased skeletal muscle mitochondrial content and an enhanced mitochondrial oxidative capacity (Zoll et al., 2002). Mitochondrial DNA is known to be reduced with the use of antiretroviral drugs such as nucleoside reverse transciptase inhibitors, with potential side-effects such as lipodystrophy insulin resistance and dislipidemia (Pinti et al., 2006). However, general antiviral exposure (%) was not a predictor in our meta-analysis. Moreover, it was previously (Sutinen and Yki-Järvinen, 2007) reported as well that there are no differences in the amount of mitochondrial DNA in skeletal muscle of those with versus without lipodystrophy. Next to this, PLWH with lipodystrophy are capable of improving muscle oxygen uptake and CRF levels, suggesting that the physiological capacity of muscles to extract and utilize oxygen is unaltered by lipodystrophy status (Ramírez-Marrero et al., 2014). In summary, the integration of cardiovascular, pulmonary, neuromuscular, and metabolic functions contributing to changes in CRF in people with versus without lipodystrophy status remains unclear and should be a topic of future research.

We also explored moderators for CRF outcomes following physical activity interventions. The current meta-analysis showed that physical activity resulted in a pooled SMD in predicted VO_2 max or VO_2 peak of 3.43 ml/min/kg (95% CI=1.82 to 5.0), in line with findings of a recent meta-analysis (O'Brien et al., 2016) in PLWH. Such improvements in CRF are of high clinical relevance. For example, among the general population, every 3.5 ml/kg/min incremental increase in VO_2 peak is associated with 13% and 15% decrements in risk of all-cause mortality and CVD respectively (Kodama et al., 2009). Our meta-analysis adds to the current knowledge that higher CD4+ count, which is indicative of a better immune response, was associated with higher levels of CRF improvement. More research is however needed to clarify associations between immune and CRF responses following physical activity. Unfortunately, due to lack of data we could not explore the effect of viral load on the CRF response. Our meta-analysis did however show that a better CRF response is obtained in response to moderate, as opposed to high intensity exercise. Previous research already indicated that moderate intensity physical activity improves the immune function in PLWH (Ezema et al., 2014; Garcia et al., 2014), while high-intensity exercise is known to have immunosuppressive effects (d'Ettorre et al., 2014). However, data should be interpreted with caution due to the very limited data available. Nonetheless, our data has for the first time provided a comprehensive meta-regression to identify factors influencing CRF in PLWH and build upon previous meta-analyses which have not conducted such analyses.

Practical implications

Improving CRF through physical activity is a feasible, realistic and clinically meaningful outcome in PLWH. Special attention should be given to those with lipodystrophy. CRF is a relatively straight-forward and low-risk measurement in clinical practice. However, consideration of the assessment method is needed when interpreting any scores. For example, our data indicate that treadmill tests predict higher CRF levels than cycle ergometer tests, an observation also found in the general population (Shephard, 1984). Sub-maximal tests, on their turn are underestimating values obtained with gold-standard measurements.

Limitations

Whilst the results are novel, some caution should be attached due to small number of studies included in some sub-analyses and due to limitations in reporting of other important variables such as specific antiviral treatments, duration of antiviral treatment, mean lean body mass loss and lifestyle factors (physical activity, smoking). Future research should focus on these treatment-related and clinical parameters. Future research should also further explore in more detail the role of physical activity characteristics, i.e. the most optimal frequency, intensity, time and type of physical activity as well as motivational considerations. In particular, immunological responses to physical activity interventions and association with CRF levels, but also with more distal outcomes such as the risk for cardiovascular diseases, diabetes, cancer and premature mortality should be explored in more detail.

Conclusion

Our meta-analysis demonstrates that PLWH, but in particular those at older age, with a higher BMI and with lipodystrophy should be considered as an important high-risk group for low CRF, an important predictor of CVD and premature mortality. More research on the most optimal physical activity intervention characteristics is needed.

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Conflict of interests

None.

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Figure 1. Flow diagram

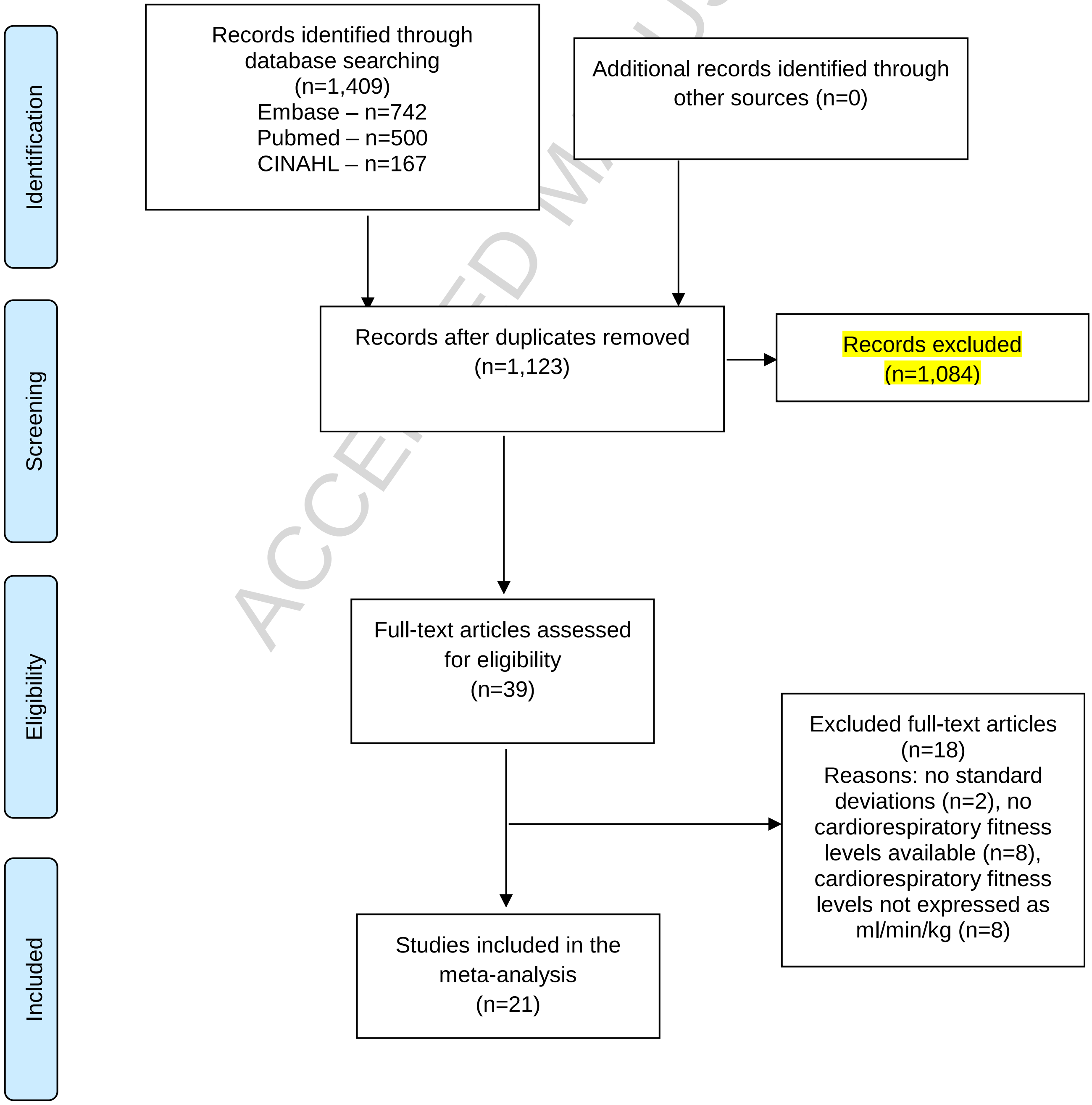

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Table 1. Characteristics of the included studies

Author	VO_2 peak /max	Assess-ment method	Cycling / running	Design	Region	Setting	Sample size	Age	% Male	% Cauca-sian	BMI	% AV	Illness duration	% T2DM	Lipo-dystr.	% current smoker	Viral load	CD4+ current	NOS score
Cutruno 2016	27.2±8.9	1	2	2	1	3	90	48	0	0.10	31		17.6		2	0.36			3
Gomes Neto 2016 [Lipodystrophy]	31.4±6.1	2	1	3	2	0	34	44.9	0.529		23	1			1			490	7
Gomes Neto 2016 [No Lipodystrophy]	30.4±7.6	2	1	3	2	0	29	40.8	0.552		23.1	1			0			598	7
Mangona 2015	32.5±7.1	2	2	1	3	0	53	40	0	0	24.1	1			2			473.6	8
Ezema 2014 [exerise group]	23.0±2.5	2	2	1	3	1	17	40.1		0	28.65				2			516	8
Ezema 2014 [control group]	24.0±2.5	2	2	1	3	1	16	32.5		0	29.01				2			492	8
Jaggers 2014	20.1±8.6	2	2	2	1	3	63	48	0.492					0.143	2				3
Ramírez-Marrero 2014 [Lipodystrophy]	26.8±1.3	2	2	3	1	3	32	50.3	0.406	0	29			0.25	1	0.55			7
Ramírez-Marrero 2014 [No Lipodystrophy]	32.2±1.5	2	2	3	1	3	28	48.1	0.536	0	26.4			0	0	0.19			7
Sullivan 2014 0.7	29.2±7.6	2	1	3	1	0	68	49.2	0.912		26.4	1	16		2			516	3
Cade 2013 [pioglitazone group]	24.3±5.2	2	2	1	1	0	12	42	0.75	0.58	30.4				2			638	7
Cade 2013 [exercise group]	23.6±5.6	2	2	1	1	0	8	41	1	0.37	29.9				2			372	7
Mapstone 2013	20.3±6.4	2	2	3	1	0	37	58.9	0.818		28.4	1	16.8	0.351	2	0.38		663	2
Raso 2013	34.2±0.9	2	2	3	2	2	39	40.6	1		24.8	0.461	6.1		2		4.4	521	7
Oursler 2009	18.4±5.6	2	2	3	1	3	43	57.5	1	0.116				0.116	2	0.63			3
Hand 2008 [male experimental group]	31.6±0.4	2	2	1	1	3	14	41.2	1						2				8
Hand 2008 [female experimental group]	31.2±0.3	2	2	1	1	3	7	41.2	0						2				8
Hand 2008 [control group]	29.4±0.3	2	2	1	1	3	19	42.4	0.84	0.316					2				8
Mutimura 2008 [no exercise group]	23.9±2.9	1	2	1	3	1	50	37.5	0.4		24.4	1			1	0.2		348	8
Mutimura 2008 [exercise group]	24.3±3.8	1	2	1	3	1	50	37.8	0.4		24	1			1	0.14		353	8

Table 1. Continued.

Author	VO_2 peak /max	Assess-ment method	Cycling / running	Design	Region	Setting	Sample size	Age	% Male	% Cauca-sian	BMI	% AV	Illness duration	% T2DM	Lipo-dystr.	% current smoker	Viral load	CD4+ current	NOS score
Dolan 2006 [exercise group]	16.9±1.0	1	1	1	1	3	20	43	0	0.35	29.3	0.85	11		2	0.35	2.3	539	7
Dolan 2006 [control group]	15.3±1.1	1	1	1	1	3	20	40	0	0.2	28.6	0.8	9		2	0.55	3	419	7
Terry 2006 [diet and exercise]	32.0±5.0	2	2	1	2	0	15	36	0.6	0.87	25	1	6		1			563	8
Terry 2006 [diet]	34.0±7.0	2	2	1	2	0	15	39	0.73	0.93	24	1	6		2			435	8
Cade 2003	24.6±1.2	2	2	3	1	0	15	41.9	0.67		26.9		7		2	0.27		430	6
Baigis 2002 [exercise group]	30.2±6.4	2	2	1	1	3	52	39	0.81	0.33					2			352	7
Baigis 2002 [no exercise group]	32.0±7.1	2	2	1	1	3	47	34.5	0.79	0.32					2			365	7
Thöni 2002	25.2±1.2	2	1	3	4	0	17	44.4	0.71		23.5	1	6.7		1		2.1	514	3
Smith 2001 [exercise group]	34.9±5.7	2	2	1	1	0	18	36.6	0.78		27.2		4		2		3.7	328	8
Smith 2001 [control group]	31.0±5.9	2	2	1	1	0	29	35.4	0.86		27.6		4.5		2		3.9	357	8
Perna 1999 [compliant group]	28.7±7.5	2	1	1	1	0	11	36.7	0.82	0.357	22.8				2			468	8
Perna 1999 [non-compliant group]	25.4±9.1	2	1	1	1	0	7	36.7	0.57	0.357	30.2				2			476	8
Perna 1999 [control group]	28.3±9.6	2	1	1	1	0	10	36.7	0.5	0.357	26.9				2			420	8
Mac Arthur 1993 [compliant group]	33.2±3.3	2	2	2	1	0	6	38.8	1						2			209	3
Mac Arthur 1993 [somewhat compliant group]	29.8±10.0	2	2	2	1	0	7	32	1						2			158	3
Mac Arthur 1993 [non compliant group]	29.7±8.3	2	2	2	1	0	12	35.5	0.83						2			104	3

VO_2 peak /max= peak / maximal oxygen uptake expressed as ml/min/kg (mean±standard deviation); assessment method: 1=a submaximal exercise test, 2=a maximal exercise test); cycling/running: 1=exercise test on a treadmill, 2=exercise test on a cycle ergometer; design: 1=randomized controlled trial, 2=one-arm pre-test post-test study, 3=cross-sectional study; region: 1= North-America, 2=South-America, 3=Africa, 4=Europe; setting:0=mixed or unknown, 1=inpatients, 2=outpatients, 3=community patients; BMI=body mass index; % AV= percentage of people on antiviral therapy; illness duration expressed in years;T2DM= type 2 diabetes mellitus; lipodystrophy: 0=0%, 1=100%, 2=unknown; Opportunistic infections:0=0%, 1=unknown; viral load expressed in log 10 copies/mL.mean CD4+ count expressed in cells/mm³; NOS=Newcastle–Ottawa Scale.

Table 2. Characteristics of the interventional studies

	Post VO_2 mean	Post VO_2 SD	Supervision	Providers	Duration (weeks)	Frequency (per week)	Intensity	Time (min)	Type
Cutruno 2016	29.0	10.0	1	1	12	4	2	60	2
Mangona 2015 [formal exercise]	38.1	7.1	1	1	13	3	3	60	2
Mangona 2015 [playful exercise]	34.8	9.9	1	1	13	3	2	60	1
Ezema 2011	30.9	4.4	1	1	8	3	2	60	1
Cade 2013	26.0	7.9	1	0	16	3	3	120	2
Hand 200	39.9	1.9	1	0	6	2	2	60	2
Mutimura 2008	24.4	2.9	1	0	26	3	2	90	2
Dolan 2006	18.4	1.0	1	1	16	3	2	120	2
Terry 2006	40.0	8.0	1	0	12	3	3	60	2
Baigis 2002	30.5	6.3	0	0	15	3	3	20	1
Thöni 2002	27.8	1.5	1	0	16	2	2	45	1
Smith 2001	33.2	5.9	1	0	12	3	3	30	1
Perna 1999 [compliant group]	32.2	7.3	1	0	12	3	3	45	1
Perna 1999 [non-compliant group]	25.5	8.8	1	0	12	3	3	45	1
Mac Arthur 1993 [compliant group]	41.2	4.9	1	1	24	3	3	40	1

Supervision: 1=yes. 0=no; provider: 1=experts (i.e. minimum a bachelor-level degree in physical therapy. exercise physiology or a similar that included education in physical activity prescription and assessment; Intensity (maximal): 1=low. 2=moderate. 3=high; Type: 1=aerobic exercise. 2=mixed.

Table 3. Subgroup analyses of cardiorespiratory fitness (expressed as ml/min/kg) in people living with HIV

Analysis	**N studies**	**N participants**	**Meta-analysis Point estimate**	**95%CI**		**I²**	**P***
Subgroup analyses							
• Maximal versus Sub-maximal testing						99.6	**<0.001**
- Maximal	31	780	28.4	27.3	29.5		
- Submaximal	5	230	21.4	18.8	23.9		
• Treadmill versus cycle ergometer test						99.6	**0.03**
- Treadmill	27	794	28.0	26.8	29.2		
- Cycle ergometer	9	216	25.1	22.8	27.4		
• Geographical region						99.6	0.09
- North-America	25	675	26.9	25.0	28.8		
- South-America	5	132	32.4	28.1	36.7		
- Africa	5	186	25.5	21.3	29.7		
- Europe	1	17	25.2	15.9	34.4		
• Setting						99.6	0.07
- Inpatients	4	133	23.8	19.2	28.4		
- Outpatients	1	39	34.2	24.9	43.5		
- Community patients	12	435	25.9	23.2	28.6		
• Design						99.6	0.53
- Interventional studies (baseline)	27	690	27.7	25.8	29.7		
- Observational studies	9	320	26.5	23.2	29.8		
• Presence of lipodystrophy						99.6	**<0.001**
- Yes	6	198	27.2	23.3	31.1		
- No	2	57	31.3	24.5	38.1		

*Significant when P<0.05

Table 4. Meta-regressions of moderators of cardiorespiratory fitness (expressed as ml/min/kg) in people living with HIV

Moderator	Number of comparisons	β	95% CI		P-value*	R^2
Mean age (years)	36	-0.31	-0.58	-0.04	**0.02**	0.02
Gender (% male)	34	0.05	-0.002	0.09	0.06	0.04
Illness duration (years)	26	-0.59	-1.59	0.30	0.19	0.34
Body mass index (kg/m^2)	12	-0.99	-1.93	-0.06	**0.04**	0.34
Ethnicity (% Caucasian)	19	0.06	-0.08	0.19	0.41	0
Smoking (%)	10	-0.16	-0.41	0.09	0.21	0
Antiviral exposure (%)	13	-0.006	-0.30	0.29	0.97	0.23
CD4+ count (mean cells/mm^3)	28	-0.01	-0.04	0.01	0.37	0
HIV load (mean log^{10} copies /mm^3	6	6.82	-0.35	13.99	0.06	0.46
Diabetes (%)	5	-0.20	-0.68	0.27	0.40	0
Lipodystrophy (presence)	8	-4.63	-7.88	-1.39	**0.005**	0.71

*Significant when P<0.05.

Table 5. Meta-regression and subgroup analyses of moderators of the cardiorespiratory fitness outcome following exercise in people with HIV

	Number of comparisons	**β**	**95% CI**		**r^2**	**p-value***
Mean age (years)	15	0.08	-0.05	0.20	0	0.25
Gender (% male)	14	0.19	-0.81	1.18	0	0.71
Illness duration (years)	5	-0.01	-0.21	0.18	0	0.87
Body mass index (kg/m²)	10	-0.04	-0.20	0.12	0	0.64
Ethnicity (% Caucasian)	10	0.04	-1.33	1.41	0	0.95
CD4+ count (mean cells/mm³)	11	0.004	0.0007	0.007	0.53	**0.016**
Physical activity intervention time (min)	15	0.004	-0.009	0.016	0	0.56
Physical activity duration (weeks)	15	-0.07	-0.14	0.01	0	0.11
	Number of comparisons	**Hedges' g**	**95% CI**		**I^2 (%)**	**p-value***
Physical activity intervention intensity					92.0	0.069
- Moderate	6	1.45	0.88	2.02	95.8	**<0.001**
- Moderate to high	9	0.43	-0.02	0.88	79.9	0.062
Physical activity frequency					92.0	**<0.001**
- 2 times per week	2	2.80	1.82	3.78	92.8	**<0.001**
- 3 times per week	12	0.61	0.25	0.96	88.4	**<0.001**
- 4 times per week	1	0.19	-0.95	1.33	0	0.75
Supervision the entire period					92.0	**0.033**
- Yes	14	0.90	0.51	1.28	92.2	**<0.001**
- No	1	0.05	-1.29	1.39	0	0.94
Qualification of the provider					92.0	0.44
- Qualified	6	1.01	0.43	1.60	91.4	**<0.001**
- Not qualified / unknown	9	0.72	0.24	1.19	92.8	**0.003**
Setting					92.0	0.47
- Inpatients	2	0.91	-0.17	1.98	96.7	0.10
- Community patients	4	1.23	0.45	2.00	96.4	**0.002**

*Significant when p<0.05. °Providers of physical activity interventions were considered experts when they had at a minimum a bachelor-level degree in physical therapy, exercise physiology or a similar qualification that included education in physical activity prescription and assessment.

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Highlights

- The treatment of people living with HIV should include a focus on cardiorespiratory fitness.
- Special attention should be given to those with lipodystrophy.
- A better cardiorespiratory fitness response is obtained following moderate as opposed to high intensity exercise.
- More research on the most optimal physical activity prescription for people living with HIV is needed.